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Myelodysplastic Features in Juvenile Rheumatoid Arthritis

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We have attempted to investigate the dysplastic changes in the hematopoietic system associated with juvenile rheumatoid arthritis (JRA) and its relation to disease activity. The peripheral blood smear and bone marrow aspiration samples of 17 JRA patients were investigated and correlations with laboratory parameters of disease activity sought. The age range was 6–16 years and the duration of disease 1.5–108 months. Abnormal finding of the peripheral smear and bone marrow were scored separately. The score of pathological peripheral blood findings correlated significantly with CRP and ferritin (both $P < 0.05$). In the bone marrow specimens marked changes were noted in the myeloid, erythropoietic, and megakaryopoietic series; however, the score of pathological findings did not correlate with laboratory parameters of disease activity ($P > 0.05$). We suggest that JRA is associated with marked myelodysplastic changes, also manifested in the peripheral blood smear; these changes may well be the consequence of the inflammatory milieu, including cytokines, during active disease. Am. J. Hematol. 54:166–169, 1997

Key words: Juvenile rheumatoid arthritis; myelodysplasia

INTRODUCTION

Juvenile rheumatoid arthritis (JRA) is an autoimmune disease accompanied by various extra-articular findings [1]. Hematological disorders, most of them in the erythroid series, have been rarely reported in rheumatoid arthritis [2–5].

A number of dysplastic changes noted in the peripheral blood and bone marrow examinations led us to investigate the nature of these changes. We present the hematological changes that we have observed in JRA patients, as well as their clinical correlations.

PATIENTS AND RESULTS

Seventeen JRA patients were the subject of this study. The age range was 6–16 years (mean: 11 years). The study included 11 girls and 6 boys. The duration of disease ranged from 1.5 to 108 months (mean: 48 ± 10). The participants had not received iron, corticosteroids, immunosuppressive drugs, or any transfusions, and none had acute infection or gross bleeding.

Clinical parameters of disease activity were assessed by C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR). The abnormal pathological findings in the peripheral blood were scored, with the presence of each abnormality scored as 1 (Table I). Abnormal features in the bone marrow (BM) were scored separately. Each feature was scored as follows: 1, mild change; 2, moderate change; and 3, severe change. The ratio of the myeloid/erythroid series, left shift, hypogranulation, or abnormal granulation of myeloid cells, nuclear dysmorphism, presence of blast-like cells, megaloblastoid alterations in granulopoietic or erythropoietic series, dysplastic maturation of erythroid precursors, erythroid hypoplasia, and various alterations in the megakaryopoietic series, plus a score of 1 was given for change in cellularity and fatty changes in the BM (Table I).

Serum iron was decreased in all patients, with a mean of 19 + 1 μg/dl. Serum iron binding capacity was within normal limits in all cases. In 11 patients, iron stores were present; in six patients, the presence of iron stores was negative. Sideroblast counts were low in all patients, with the lowest values in those without iron stores (mean:

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TABLE I. Peripheral Smear Findings in JRA Patients and Scores of Abnormal Findings in Peripheral Smear and Bone Marrow*

Case No.	Hb (g/dl)	MCV (fl)	MCHC (g/dl)	WBC ($\times 10^9$/L)	PNL (%)	Pelger-Huet PNL (%)	Hypersegmentation (%)	Toxic granulation PNL (%)	Thrombocyte ($\times 10^9$/L)	Giant thrombocyte	P.S.[a] score	BM score[b]	Marrow iron
1	9.2	55	27	8,900	75	1	17	+33	703		8	6	+
2	10.0	69	32	8,700	73	2	7		276		6	2	+
3	10.6	79	34	19,400	80			+33	520	+	6	14	+
4	9.9	79	33	6,000	55	2	20		342	+	4	16	+
5	9.6	67	19	7,100	55		11		458		5	11	−
6	9.1	68	29	15,800	74	2	13		538		8	12	+
7	10.4	63	33	11,000	63	1			494		5	8	+
8	8.0	66	31	4,900	55				420	+	4	11	−
9	7.12	60	29	5,000	77		8				5	13	−
10	10.7	66	29	10,200	62			+35	580		6	13	+
11	8.6	83	35	4,900	88	2			293	+	4	9	−
12	10.1	72	32	9,800	70	5		+60	415		6	11	+
13	9.6	66	34	18,800	84	2			611	+	7	13	+
14	9.7	78	31	14,000	40	2			625		4	12	−
15	9.5	58	28	14,700	87		10	+41	909		8	11	−
16	9.8	68	34	19,700	80				861		5	5	+
17	7.1	54	21	15,600	70				448	+	6	2	+

*Normal limits: hemoglobin (Hb) lower limit: 11.5 g/dl; MCV lower limit: 77 fl; MCHC lower limit: 33 g/dl; white blood cell (WBC) count upper limit: 14.5×10^9/L; percentage of PNL upper limit: 60%; thrombocyte count upper limit: 450/L.

[a]Score of abnormal findings in peripheral blood smear.

[b]Score of abnormal findings in bone marrow.

$9 \pm +2$). Serum vitamin B_{12}, folic acid, and reticulocyte counts were normal in all cases. Erythropoietin levels were increased in six patients. The direct Coombs test was negative in all. The mean serum ferritin level was 284 ± 87, with a range of 16–1,000 ng/ml.

BM examination of all cases showed normal maturation coexisting with abnormal maturation at different levels (Fig. 1). Fatty changes were present in seven patients, and BM cellularity was increased in five patients. Erythroid hypoplasia was present to a mild and moderate degree in eight and three patients, respectively. Follow-up BM specimens in four patients examined at a stage of clinical remission did not show any blastic changes.

The scores for pathological peripheral blood findings correlated significantly with CRP values ($r = 0.54$; $P = 0.03$). However, the scores for abnormal BM features did not correlate with CRP vlaues ($P > 0.05$). There was also a correlation of ferritin with the peripheral blood score ($r = 0.54$; $P = 0.04$) but not with BM findings score ($r = 0.29$; $P = 0.29$). A significant correlation was noted between CRP and ferritin ($r = 0.54$; $P = 0.037$).

DISCUSSION

We have described qualitative and quantitative dysplastic hematopoietic features in 17 JRA patients with anemia. In 24% of our patients, anemia was associated with both chronic disease and iron deficiency, in agreement with the literature [1–3].

Since none of the patients had any infections at examination, abnormal peripheral smear findings, such as leukocytosis, and toxic granulation, were atrributed to JRA, per se. Furthermore, a significant correlation was found between the abnormal peripheral findings and disease activity markers.

Abnormal quantitative findings have been prominent in the BM specimens. An increase in the myeloid series, a suppression in the erythroid series, and a mild to moderate increase in the megakaryocytic series have been seen. These changes may be explained as a marrow response (in the form of myeloid and megakaryocytic increase) to the suppression in erythroid series. However, significant qualitative changes were present as well. The most manifest morphological alterations were in the myeloid series, as displayed in Figure 1. In the erythroid series, megaloblastoid changes and nuclear dysmorphism were present. The hypoplastic trend in the erythroid series with a lack of erythroid hyperplasia suggests that inhibition of erythropoiesis may be effective in the anemia of these patients. Erythroid hypoplasia has manifested as anemia, whereas the increase in the myeloid and megakaryocytic series has manifest in the periphery in the form of leukocytosis and thrombocytosis.

In JRA, drugs may be held responsible for the dysplastic changes. However, although four patients had received no medications, marked alterations were present in their BM as well. Myelodysplastic changes were previously reported in two patients with rheumatoid arthritis (RA), one of whom treated with methotrexate [6]. By contrast, in patients with myelodysplastic syndrome (MDS), there

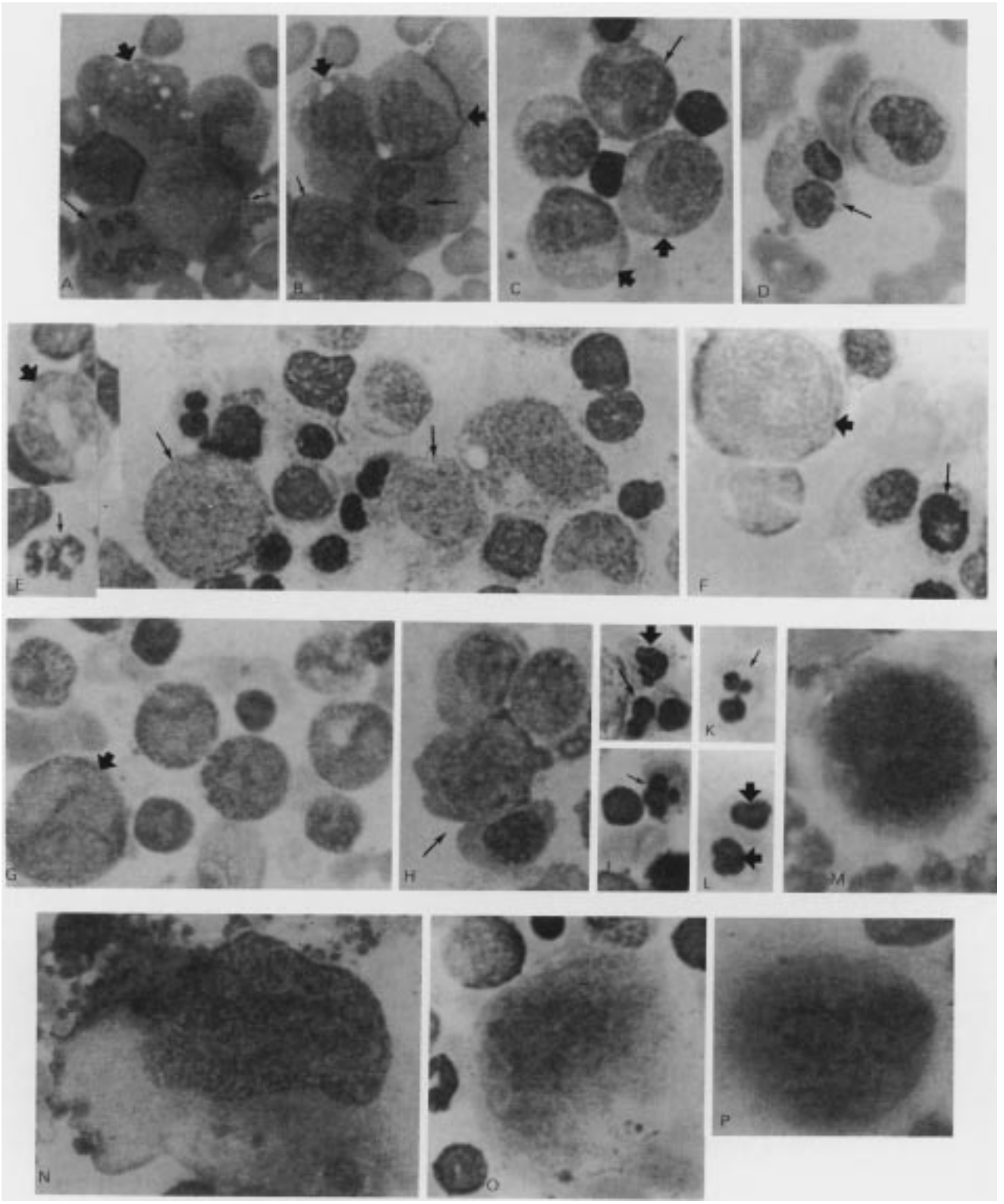

Fig. 1. A: abnormal nucleated giant pnl (*small arrow*); A,B: blast-like cells with nuclear dysmorphism, nucleoli, and vacuoles (*large arrow*) and cells with characteristics of both monocytes and myelocytes with some degree of hypogranulation (*tiny arrow*); C: hypogranulated myeloid cells (*large arrow*); B,D: Pergel-Huet-like cell (*small arrow*); E: hypogranulated giant metamyelocyte (*large arrow*), abnormally nucleated pnl (*tiny arrow*), promyelocyte and myelocyte with nucleoli (*small arrow*); F: megaloblastoid promyelocyte (*large arrow*), cell with chromatin condensation (*small arrow*); G: left shift of myeloid series, promyelocyte with abnormally distributed granules (*large arrow*) H: megaloblastoid erythroid cell (*small arrow*); I–L: dysplastic maturing erythroid precursors with nuclear irregularities (*large arrow*) multinucleation (*tiny arrow*) and unequal binucleation (*small arrow*); M: small megakaryocyte almost filled with nucleus; N: hypolobate nuclei of megakaryocyte; O: anucleate fragment of megakaryocyte cytoplasm; P: monolobate megakaryocyte.

are rare reports of RA; it has been suggested that this might have been merely coincidental or that the RA might have developed on the basis of the immune abnormalities of MDS [7].

In this study, the changes in the peripheral smear and bone marrow suggested dysplasia. The parameters of clinical disease activity correlated with the dysplastic changes in the periphery, whereas there was not a significant correlation with the dysplastic score of the BM. No correlation was present between the duration of the disease and the presence of abnormal findings, and it was noteworthy that hypocellularity was not present in the periphery.

CONCLUSIONS

The aforementioned changes imply that dysplasia may be an effective factor in the anemia of JRA. We have been unable to elucidate the pathophysiological mechanism(s) underlying the hematopoietic dysplasia of JRA. It has been proposed that cellular immune system dysfunction leads to alteration of the microenvironment of the bone marrow via abnormally regulated cytokines and other local intracellular messengers [8,9]. Further follow-up evaluation of selected patients with BM examinations may shed light on the causes and prognostic significance of the hematopoietic dysplasia in these patients.

REFERENCES

1. Cassidy JT, Ross EP: Juvenile rheumatoid arthritis. In Cassidy JT, Petty RE (eds): "Textbook of Pediatric Rheumatology," Ed 2. New York: Churchill Livingstone, 1990.
2. Koerper MA, Stempel DA, Dallman PR: Anemia in patients with juvenile rheumatoid arthritis. J Pediatr 92:930, 1978.
3. Stockman JA: Hematologic manifestations of systemic diseases. In Nathan D, Oski FA (eds): "Textbook of Hematology of Infancy and Childhood," Ed 3. Philadelphia: WB Saunders, 1987.
4. Ewer AK, Darbyshier PJ, Southwood TR: Systemic onset juvenile rheumatoid arthritis. Am J Dis Child 132:760, 1978.
5. Kirel B, Yetgin S, Saatçi U, Ozen S, Bakkalog lu A, Besbas N: Anemia in juvenile rheumatoid arthritis. Clin Rheumatol 15:236, 1996.
6. Rosenthal NS, Farhi DC: Bone marrow findings connective tissue disease. Am J Clin Pathol 92:650, 1989.
7. Mufti GJ, Figes A, Hamblin TJ, Oscier DG, Copplestone JA: Immunologic abnormalities in myelodysplastic syndrome. 1. Serum immunoglobulins and autoantibodies. Br J Haematol 63:143, 1986.
8. Louache F, Henri A, Bettaieb A, Oksenhendler E, Raguin G, Tulliez M, Vainchenker W: Role of human immunodeficiency virus replication in vitro growth of hematopoietic progenitors. Blood 80:2991, 1992.
9. Clatch RJ, Krigman HR, Peter MG, Zutter MM: Dysplastic haemopoiesis following orthotopic liver transplantation: Comparison with similar changes in HIV infection and primary myelodysplasia. Br J Haematol 88:685, 1994.